PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Tapas Mukhopadhyay, *et al.*

Serial No.: 10/043,877

Filed: January 9, 2002

For: ANTIHELMINTHIC DRUGS AS A TREATMENT FOR HYPERPROLIFERATIVE DISEASES

Group Art Unit: 1642

Examiner: Brandon J. Fetterolf

Atty. Dkt. No.: INRP:095US

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May 21, 2007 Tamara Kale

REPLY BRIEF

TABLE OF CONTENTS

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REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants hereby submit an original and two copies of this Reply Brief in response to the Examiner's Answer. The due date for this Reply Brief is May 23, 2007, in view of the mailing of the Examiner's Answer on March 23, 2007.

No fees are believed due in connection with this paper. However, should any other fees be due, or the attached fee is deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski L.L.P. Deposit Account No. 50-1212/INRP:095US.

I. REAL PARTY IN INTEREST

The real parties in interest are the assignee, The Board of Regents, The University of Texas System and the exclusive licensee, Introgen Therapeutics, Inc.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences for related cases.

III. STATUS OF THE CLAIMS

Claims 1-182 were originally filed January 9, 2002.

In a Response to Restriction Requirement dated March 29, 2004, Appellants filed an amendment in which claims 4-8, 11, 30-74, 78-82, 107-160, 163, 166, 168 and 171-175 were withdrawn from consideration as being drawn to a non-elected invention and/or species and claims 1-29, 75-106, 161-162, 164-167 and 169-182 were elected for prosecution.

Claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162, 164-165, 167, 169-170 and 176-182 were rejected in the Office Action dated June 28, 2004.

In a Response to Office Action dated October 28, 2004, Appellants filed an amendment in which claims 164-165, 167, 169-170 and 176-182 were cancelled without prejudice or disclaimer, and in which 22, 100, 161 and 162 were amended.

Claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162 and 164 were rejected in the Office Action dated March 18, 2005.

In a Response to Office Action dated July 18, 2005, Appellants filed an amendment in which claims 161-162 were amended and new claims 183-184 were added.

Claims 1-3, 9, 12-19, 21-29, 75-77, 83-97, 99-106, 161-162 and 183-184 were rejected in the Office Action dated November 16, 2005.

In a Response to Office Action dated April 17, 2006, Appellants filed an amendment in which claims 2, 10-11, 13, 15, 17-22, 29-30, 32, 64, 76-86, 88, 90-100, 107 and 109 were amended, and in which claims 1, 9, 12, 64, 75, 161-162, 164-165, 167, 169-170 and 176-184 were cancelled without prejudice or disclaimer.

Claims 2-8, 10-11, 13-63, 65-74, 76-160, 163, 166, 168, 171-175 were pending at the time of the Office Action dated July 10, 2006, with claims 4-8, 11, 30-63, 65-74, 78-82, 107-160, 163, 166, 168 and 171-175 withdrawn and claims 2-3, 10, 13-19, 21-29, 76-77, 83-97 and 99-106 standing rejected. Thus, claims 2-3, 10, 13-20, 21-29, 76-77, 83-97 and 99-106 are on appeal and the subject of this appeal brief.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

In one general aspect, as recited in claim 22, the present invention concerns a method for inducing apoptosis in a tumor cell expressing a tumor suppressor gene, by determining the status of the tumor suppressor gene status of the tumor cell and administering an effective amount of a benzimidazole to the tumor cell, wherein expression of the tumor suppressor gene by the tumor cell and benzimidazole results in the apoptosis of the tumor cell. *See, e.g.*, p. 8, lines 19-23; p. 15, lines 19-28; and Example 2 at p. 56, line 13 through p. 64, line 12.

In another general aspect, as recited in claim 100, the present invention concerns a method for treating a patient having cancer, wherein cancer cells express a tumor suppressor, by determining the tumor suppressor gene status of the cancer cells and administering an effective amount of a benzimidazole to the patient where the expression of the tumor suppressor gene by

the cancer cell and the administration of the benzimidazole results in the inhibition of the cancer. *See, e.g.*, p. 4, lines 28-31, p. 5, lines 15-18; and p. 14, lines 24-27.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1) Are claims 76, 83-97 and 99-106 properly rejected as being unpatentable over Camden (U.S. Patent No. 6,262,093, "Camden I") in view of Perdomo *et al.*, *J. Cancer Res. Clin. Oncol.*, 124:10-18, 1998 ("Perdomo") under 35 U.S.C. § 103(a)?

2) Are claims 76-77, 83-97 and 99-106 properly rejected as being unpatentable over Camden I in view of Perdomo in further view of Delatour *et al.*, *Therapie*, 31:505-515, 1976 ("Delatour") under 35 U.S.C. § 103(a)?

3) Are claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106 properly rejected as being unpatentable over Camden (U.S. Pat. No. 5,880,144, "Camden II") as evidenced by Camden I in view of Perdomo under 35 U.S.C. § 103(a)?

4) Are claims 3 and 77 properly rejected as being unpatentable over Camden II in view of Perdomo in further view of either Delatour or Nasr *et al.*, *J. Pharm. Sci.*, 74:831-836, 1985 ("Nasr") under 35 U.S.C. § 103(a)?

5) Are claims 13-14 and 86-87 properly rejected as being unpatentable over Camden II in view of Perdomo and further in view of Lucci *et al.*, *Cancer*, 86:300-311, 2000 ("Lucci") under 35 U.S.C. § 103(a)?

VII. REPLY

In response to each of Appellants' arguments countering the several obviousness rejections, the Examiner in the Examiner's Answer ("the Answer") primarily asserts that Appellants have considered each of the references individually, rather than as a whole as required by case law. While Appellants generally dispute this characterization, this Reply Brief focuses on countering the

Examiner's legally faulty and unsupported arguments regarding his refusal to consider the Third Declaration by Tapas Mukhopahdyay, Sunil Chada, Abner Mhashilkar and Jack A. Roth Under 37 C.F.R. § 1.131 ("the Third Declaration") (Exhibit 5) with respect to the obviousness rejection of claims 76, 83-97 and 99-106 over Camden I (Exhibit 1) in view of Perdomo (Exhibit 2) and the obviousness rejection of claims 76-77, 83-97 and 99-106 over Camden I in view of Perdomo in further view of Delatour (Exhibit 7).

A. Factual Background

In response to the two obviousness rejections based on Camden I, Appellants submitted the Third Declaration to demonstrate that the *in vivo* cancer treatment aspect of the presently claimed invention was conceived and reduced to practice before the filing date of Camden I. In the Office Action dated July 10, 2006 ("the July 2006 Office Action") (Exhibit 6), the Examiner asserted that Camden I "is a U.S. patent or U.S. patent application publication of a pending or patented application that claims the rejected invention or an obvious variant." July 2006 Office Action, p. 2. The Examiner provided no basis for this accusation in the July 2006 Office Action. In the Appeal Brief, Appellants argued that a two-way test of unpatentability is the proper standard to analyze the propriety of the Examiner's contention that the subject matter of the presently claimed invention and the invention of Camden I were the "same" or "obvious variants" of each other. Appeal Brief, pp 6-7. Although not required to do so, Appellants further provided arguments that under the two-way test, the inventions were not the same or obvious variants. Appeal Brief, pp 7-13.

In the Answer, the Examiner cites MPEP § 804 for the assertion that a one-way test is the proper paradigm to analyze whether the inventions of Camden I and that of the present claims are the same or obvious variants. Answer, p. 12. While the Examiner concludes that a one-way test is proper, the Examiner provides no analysis of Camden I and the presently claimed

invention under this test. The justification for failing to supply any analysis as to how the two inventions are supposedly the same or obvious variants of each other is stated in the Answer at p. 13:

> Moreover, the Examiner recognizes that it is important to note that this is not a rejection and accordingly is not required, *per se*, to clearly set forth any analysis as stated by Appellants. In the instant case, it is the Examiner's opinion that a statement such as "the reference is claiming the same patentable invention or are obvious variants" is sufficient for said reasoning.

In the July 2006 Office Action and echoed again in the Answer, the Examiner refused to consider the Third Declaration on the basis that a declaration under 37 C.F.R. § 1.131 is inappropriate when the reference is claiming the same patentable invention or an obvious variant. July 2006 Office Action, pp 12-13; Answer, pp 12-13. In both the July 2006 Office Action (p. 2) and the Answer (p. 13), the Examiner cited two sections of the MPEP to support this reasoning: MPEP §§ 608 and 2306. The Examiner concluded that Camden I, if not commonly owned, may only be overcome by establishing priority of invention through an interference proceeding. July 2006 Office Action, p. 2; Answer, p. 13. As such, the Third Declaration has not been considered by the Examiner at this time.

B. The Examiner's Assertion That the Present Claims and the Invention of Camden I Are the "Same Patentable Invention or an Obvious Variant Thereof" Is Legally Faulty and Unsupported

Contrary to the Examiner's conclusion that a one-way test of unpatentability is the proper measure of whether the claims of a pending application and those of a U.S. patent are interfering, the Code of Federal Regulations and case law have firmly established that a two-way test is proper. "An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party **and *vice versa***." 37 C.F.R. § 41.203(a) (emphasis added); *Winter v. Fujita*, 53 USPQ2d 1234, 1243 (BPAI 1999) ("Resolution of an interference-in-fact issue involves a two-way patentability

analysis."). Thus, in order to determine if interfering subject matter exists, a ***two-way*** analysis of patentable distinction must be performed.

The Examiner's reliance on MPEP § 804 for the proposition that a one-way test is appropriate does nothing to support his argument. This section, entitled "Definition of Double Patenting," is drawn to double patenting issues. A double patenting issue is ***not*** the same as an interference issue. In contrast to an interference situation, discussed above, MPEP § 804 sets forth the following requirements before a double patenting issue may arise:

> Before consideration can be given to the issue of double patenting, two or more patents or applications must have at least one common inventor and/or be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3) pursuant to the CREATE Act (Pub. L. 108-453, 118 Stat. 3596 (2004)).

Not only are the facts that may give rise to double patenting not in play here, but the Examiner has not issued a double patenting rejection. Thus, double patenting is irrelevant. To the extent, then, that the Examiner relies on MPEP § 804 to contend that a one-way test of unpatentability is appropriate to examine the claimed inventions of Camden I and the present invention, the argument is unavailing.

An Examiner is required to set clearly forth reasons for any rejection. *See* 37 C.F.R. § 1.104; 35 U.S.C. § 132. Although the Examiner provides reasoning (albeit, incorrect reasoning) that a one-way test is appropriate for analyzing allegedly interfering subject matter, ***no analysis*** of the allegedly interfering subject matter is presented in either the July 2006 Office Action or the Answer. The Examiner's "analysis" consists only of the statement that it is his "opinion" that the subject matter is interfering. Answer, p. 13. In this conclusory statement, the Examiner has failed to "properly communicate the basis for a rejection," as instructed by MPEP § 706.02(j). *See also* MPEP § 2142 (an examiner bears the burden of establishing a *prima facie* case of obviousness).

The Examiner justifies solely relying on his opinion by stating that "this is not a rejection and accordingly [he] is not required, *per se*, to clearly set forth any analysis." Answer, p. 13. The Examiner provides no reasoning or legal precedent for either the proposition that no rejection is at hand, or that because no rejection is at hand, his "opinion" is sufficient to conclude that interfering subject matter exists between Camden I and the presently claimed invention. Appellants cannot discern how the conclusion that the subject matter of Camden I and the presently claimed invention is interfering is unrelated to a rejection, particularly in view of the fact that the Examiner's refusal to consider the Third Declaration—which was submitted to overcome two obviousness rejections—is based on this conclusion. While the Examiner's belief that the subject matter of Camden I and the presently claimed invention is interfering is not a direct reason ***for*** the rejections, this belief is still the basis for ***maintaining*** the rejections. "A decision to ***make or maintain*** an obviousness rejection in the face of all the evidence must ***show*** that it was based on the totality of the evidence." MPEP § 2142. This has not been done. Accordingly, the Examiner must supply the reasoning behind his conclusion that interfering subject matter is an issue.

C. The Examiner's Refusal to Consider the Third Declaration by Tapas Mukhopahdyay, Sunil Chada, Abner Mhashilkar and Jack A. Roth Under 37 C.F.R. § 1.131 Is Unjustified

As mentioned above, based on his "opinion" that the subject matter of Camden I and the present invention interferes, the Examiner continues to refuse to consider the Third Declaration. Answer, pp 12-13. The Examiner reiterates the statement first recited in the July 2006 Office Action that "an affidavit or declaration is inappropriate under 37 C.F.R. 1.131(a) when the reference is claiming the same patentable invention or are obvious variants." *Id.* To support this conclusion, the Examiner cites to MPEP §§ 608 and 2306. *Id.* at p. 13; July 2006 Office Action, p. 2. However, these sections have ***nothing*** to do with such declarations in this or any other

context. MPEP § 608 is entitled "Disclosure," and relates to the "Parts, Form, and Content of Application" of section 600. MPEP § 2306, entitled "Secrecy Order Cases," relates to the prosecution of an application under interference proceedings. These sections are completely irrelevant to the Examiner's argument.

While the proper MPEP section relating to declarations in the context of interfering subject matter is MPEP § 715, this does not detract from the fact that the Third Declaration must be considered. As described in detail in the Appeal Brief, Camden I does not claim the same patentable invention or an obvious variant of the present invention. Thus, no barrier prevents the Examiner from considering the Third Declaration.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the Examiner erred in failing to consider the Third Declaration and address its impact on the rejections under 35 U.S.C. § 103(a). It is respectfully submitted, in light of the arguments above and those set forth in the Appeal Brief, that none of the pending claims are properly rejected. Reversal of the pending grounds for rejection is thus respectfully requested.

Respectfully submitted,

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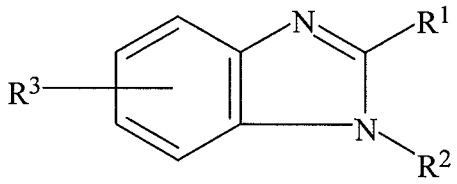
Date: May 21, 2007

VIII. CLAIMS APPENDIX

2. (Previously Presented) The method of claim 22, wherein the benzimidazole is a derivative having the formula:



wherein R^3 is selected from the group consisting of H, carboxyl ($-CO_2H$), hydroxyl, amino, chloro, difluormethoxy, benzoyl, phenyl-thio, pyridinyl, propyl-thio, diphenyl, methoxy, fluorophenylmethyl-2-chloro, propenyl, chloropropyl or esters ($-CO_2R^4$) wherein R^4 is selected from the group consisting of alkoxy, haloalkyl, alkenyl, and cycloalkyl, wherein the alkyl groups have from 1 – 8 carbons, or $CH_3CH_2(OCH_2CH_2)_n–$, or $CH_3CH_2CH_2(OCH_2CH_2CH_2)_n—$, or $(CH_3)_2CH(OCH(CH_3)CH_2)_n—$, wherein n is from 1 – 3, wherein R^1 is OH, Cl, SH, (methoxy-dimethyl pyridinyl)methyl-(sulfonyl), carbamate or piperidin-4-yl, and R^2 is hydrogen, α-methylvinyl, 3-chloropropyl or piperidin-4-yl, or the pharmaceutically effective organic or inorganic salts thereof, or mixtures thereof.

3. (Original) The method of claim 2, wherein the benzimidazole derivative is methyl 5-benzoylbenzimidazole-2-carbamate (mebendazole).

10. (Previously Presented) The method of claim 22, wherein benzimidazole administration is repeated at least once.

13. (Previously Presented) The method of claim claim 22, wherein the tumor cell is a multidrug resistant tumor cell.

14. (Original) The method of claim 13, wherein the multidrug resistant tumor cell is a lung tumor cell, a non-small cell lung carcinoma cell, a breast cancer cell, or a sarcoma cell.

15. (Previously Presented) The method of claim 22, wherein the tumor cell is a lung tumor cell.

16. (Original) The method of claim 15, wherein the lung tumor cell is a non-small cell lung carcinoma cell.

17. (Previously Presented) The method of claim 22, wherein the tumor cell is a breast cancer cell.

18. (Previously Presented) The method of claim 22, wherein the tumor cell is a sarcoma cell.

19. (Previously Presented) The method of claim 22, wherein the tumor suppressor gene is *p53*, p16, p21, Rb, p15, BRCA1, BRCA2, zac1, p73, ATM, HIC-1, DPC-4, FHIT, NF2, APC, DCC, PTEN, ING1, NOEY1, NOEY2, PML, OVCA1, MADR2, WT1, 53BP2, IRF-1, MDA-7 and C-CAM.

21. (Previously Presented) The method of claim 22, wherein the tumor suppressor gene is *p53*.

22. (Previously Presented) A method for inducing apoptosis in a tumor cell expressing a tumor suppressor gene, comprising the steps of:

(1) determining the tumor suppressor gene status of the tumor cell; and

(2) administering an effective amount of a benzimidazole to said tumor cell, wherein expression of the tumor suppressor gene by the tumor cell and benzimidazole results in the apoptosis of the tumor cell.

23. (Original) The method of claim 22, wherein determining comprises Southern blotting.

24. (Original) The method of claim 22, wherein determining comprises Northern blotting.

25. (Original) The method of claim 22, wherein determining comprises PCR.

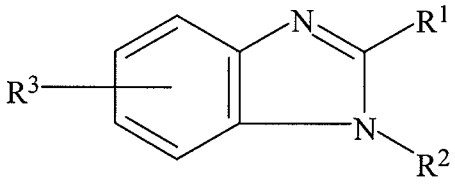
26. (Original) The method of claim 22, wherein determining comprises ELISA.

27. (Original) The method of claim 22, wherein determining comprises Western blotting.

28. (Original) The method of claim 22, wherein determining comprises immunofluorescence.

29. (Previously Presented) The method of claim 22, wherein the tumor cell expresses a functional tumor suppressor gene.

76. (Previously Presented) The method of claim 100, wherein the benzimidazole is a derivative having the formula:



wherein R^3 is selected from the group consisting of H, carboxyl ($-CO_2H$), hydroxyl, amino, chloro, difluormethoxy, benzoyl, phenyl-thio, pyridinyl, propyl-thio, diphenyl, methoxy, fluorophenylmethyl-2-chloro, propenyl, chloropropyl or esters ($-CO_2R^4$) wherein R^4 is selected from the group consisting of alkoxy, haloalkyl, alkenyl, and cycloalkyl, wherein the alkyl groups have from 1 – 8 carbons, or $CH_3CH_2(OCH_2CH_2)_n-$, or $CH_3CH_2CH_2(OCH_2CH_2CH_2)_n—$, or $(CH_3)_2CH(OCH(CH_3)CH_2)_n—$, wherein n is from 1 – 3, wherein R^1 is OH, Cl, SH, (methoxy-dimethyl,pyridinyl)methyl-(sulfonyl), carbamate or piperidin-4-yl, and R^2 is hydrogen, α-methylvinyl, 3-chloropropyl or piperidin-4-yl, or the pharmaceutically effective organic or inorganic salts thereof, or mixtures thereof.

77. (Previously Presented) The method of claim 100, wherein the benzimidazole derivative is methyl 5-benzoylbenzimidazole-2-carbamate (mebendazole).

83. (Previously Presented) The method of claim 100, wherein the tumor suppressor gene is *p53*, p16, p21, Rb, p15, BRCA1, BRCA2, zac1, p73, ATM, HIC-1, DPC-4, FHIT, NF2, APC,

DCC, PTEN, ING1, NOEY1, NOEY2, PML, OVCA1, MADR2, WT1, 53BP2, IRF-1, MDA-7 and C-CAM.

84. (Previously Presented) The method of claim 100, wherein the tumor suppressor gene is MDA-7.

85. (Previously Presented) The method of claim 100, wherein the tumor suppressor gene is *p53*.

86. (Previously Presented) The method of claim 100, wherein the cancer cell is a multidrug resistant tumor cell.

87. (Original) The method of claim 86, wherein the multidrug resistant tumor cell is a lung tumor cell, a non-small cell lung carcinoma cell, a breast cancer cell, or a sarcoma cell.

88. (Previously Presented) The method of claim 100, wherein the cancer cell is a lung tumor cell.

89. (Original) The method of claim 88, wherein the lung tumor cell is a non-small cell lung carcinoma cell.

90. (Previously Presented) The method of claim 100, wherein the cancer cell is a breast cancer cell.

91. (Previously Presented) The method of claim 100, wherein the cancer cell is a sarcoma cell.

92. (Previously Presented) The method of claim 100, wherein benzimidazole administration comprises intratumoral administration.

93. (Previously Presented) The method of claim 100, wherein benzimidazole administration comprises systemic administration.

94. (Previously Presented) The method of claim 100, wherein benzimidazole administration comprises oral administration.

95. (Previously Presented) The method of claim 100, wherein benzimidazole administration comprises administration in the area local to a tumor in said patient.

96. (Previously Presented) The method of claim 100, wherein benzimidazole administration comprises administration in the area regional to a tumor in said patient.

97. (Previously Presented) The method of claim 100, wherein benzimidazole administration is repeated at least once.

99. (Previously Presented) The method of claim 100, wherein the dose of benzimidazole is about 1.0 mg per kg body weight.

100. (Previously Presented) A method for treating a patient having cancer, wherein cancer cells express a tumor suppressor, comprising the steps of:

(1) determining the tumor suppressor gene status of the cancer cell; and

(b) administering an effective amount of a benzimidazole to said patient, wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer.

101. (Original) The method of claim 100, wherein determining comprises Southern blotting.

102. (Original) The method of claim 100, wherein determining comprises Northern blotting.

103. (Original) The method of claim 100, wherein determining comprises PCR.

104. (Original) The method of claim 100, wherein determining comprises ELISA.

105. (Original) The method of claim 100, wherein determining comprises Western blotting.

106. (Original) The method of claim 100, wherein determining comprises immunofluorescence.

IX. EVIDENCE APPENDIX

Exhibits were submitted with the Appeal Brief filed December 8, 2006.

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings.